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Food and Drug Administration
Rockville MD 20857

CBER -99-007

WARNING LETTER

DEC 7 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ms. Lisa Larson
Manager, Quality Assurance and Regulatory Affairs
Dominion Biologicals Limited
5 Isnor Drive
Dartmouth, Nova Scotia
Canada B3B1M1

Dear Ms. Larson:

An inspection of Dominion Biologicals Limited, 5 Isnor Drive, Dartmouth, Nova Scotia, Canada, was conducted from August 17 through September 1, 1998. During the inspection, violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Subchapter F, Parts 600-680, and Subchapter H, Part 820 were documented as follows:

1. Failure to establish, maintain, and follow procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(c) and 660.20(a)] in that:
 - a. the _____ heating/ventilation/air conditioning (HVAC) systems have not been validated.
 - b. environmental monitoring is not performed in the → Vialing Rooms used for filling of product.
 - c. microbial monitoring of production personnel in the Vialing Rooms and the Monoclonal Production Room is not performed.
 - d. your standard operating procedures (SOPs) #L-012-0395-03 entitled "Environmental Monitoring" and #I-012-0395-01 entitled "Bioburden Monitoring of Vialing Operations" are inadequate in that the SOPs do not describe the corrective actions to be taken when microbial action levels are exceeded on settling plates exposed during routine microbial monitoring or during vialing operations. For example, the SOPs do not require

identification of isolated microorganisms or documentation of corrective action taken. SOP #I-012-0395-01 does not address disposition of product during investigation of out of specification results.

- e. air pressure differential is not monitored in the manufacturing areas, including the Vialing Rooms and the Monoclonal Production Room.
- f. growth promotion testing is not performed on media used for sterility testing of final product, in-process testing of cell cultures, environmental monitoring, and media fill qualifications.
- g. final mixing of _____ of _____ was observed being performed in a hallway in front of doors leading into the chemical and component warehouse. The mixing time for this procedure is approximately _____. Employees were observed continually entering and exiting the warehouse through the doors where the mixing was being performed. The _____ was contained in a _____ barrel that was uncovered.

2. Failure to establish, maintain, and follow procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e) and 660.20(a)] in that:

- a. installation, operation, and performance qualification of the _____ (_____ water purification systems have not been performed.
- b. your SOP #H-012-0996-01 entitled "Routine Monitoring of the Water Supply Systems" does not specify a routine sanitization schedule for the _____ water purification systems. Furthermore, your SOP does not specify a routine maintenance schedule for changing the _____ filter on the _____ water purification system.
- c. the _____ filtration method described in your SOP #L-031-0994-00 entitled "Bioburden Monitoring of Water Systems" has not been validated.
- d. drain lines from the _____ water purification system and the water _____ used for production water, empty directly into a sewer drainpipe without any means of preventing backflow.
- e. written SOPs do not require identification of microorganisms isolated from the _____ water purification systems.
- f. written SOPs do not address corrective action to be taken when microbial action limits for the _____ water purification systems have

been exceeded and do not address disposition of product during investigation of out of specification results.

- g. although management stated that it is the policy of your firm to flush the _____) point of use sites for _____ prior to collecting water for QA testing and laboratory/production use, there is no written procedure instructing operators to flush the _____ point of use sites for _____ prior to use. During the inspection, an operator was observed filling a flask with water from the DI point of use without first _____

3. Failure to establish, maintain, and follow procedures for implementing corrective and preventative action including requirements for investigating the cause of nonconforming product and identifying the action(s) needed to correct and prevent recurrence of nonconformities and other quality problems [21 CFR 820.100] in that:

- a. investigations into nonconformities are not always complete in that the cause of the nonconformities is not always documented. For example, Non-Conformance Reports (NCRs) #98-004, #98-005, #98-007, #98-010, #98-011, and #98-012 relate to Reagent Red Blood Cells lot #P0106 in which vial #1 was found to be hemolyzing. The hemolysis was attributed to microbial contamination; however, the identity and source of the causative microorganism was not determined and possible impact of the contamination on other product was not assessed.
- b. the cause of sterility failures for _____ sublots of _____ were not determined and the causative organism was not identified. Failed sublots were reclaimed by manufacturing.
- c. documentation of the investigation of nonconformances is not always complete. For example:
- 1) NCR #97-389 (dated August 20, 1997) does not include documentation of the product name or lot number.
 - 2) NCR #97-051 (dated February 12, 1998) does not include documentation of the product lot number.
- d. SOPs are not always revised to reflect changes recommended in response to nonconformities. For example:
- 1) NCRs #97-393 (dated August 21, 1997), #97-399 (dated August 21, 1997), #97-421 (dated September 16, 1997), and #97-449 (dated October 23, 1997) document nonconformities related to weakened expression of the

A antigen on reagent red cells. Corrective action recommended included “new methods” to detect weak A₂ antigen on reagent cells. Although documentation exists indicating these new test methods are in use, affected SOPs have not been revised to reflect modifications to the test method.

- 2) NCR #97-440 (dated October 6, 1997) documents the shipment of non-licensed product to a U.S. customer. Recommended corrective action included modification of shipping procedures to require review of shipments by the Customer Service Manager or a delegate. The affected SOP #M-003-0397-02 entitled “Order Packaging and Shipping” has not been revised to reflect the recommended procedural change.

- e. no investigation is performed when biological indicators exhibit positive results following sterilization checks of the _____. For example, no investigation was performed or corrective action taken when sterilization checks performed on January 28, 1998 and March 4, 1998 failed. In both instances, the sterilization checks were merely repeated.
4. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications [21 CFR 820.70(a)] in that:
 - a. preservative effectiveness testing has not been performed for your products.
 - b. bacteriostasis/fungistasis testing has not been performed for your products.
 - c. heat distribution studies have not been performed on the _____ used to sterilize vials, forceps, and other equipment utilized during vialing operations.
 - d. sterile filtered bulk antisera and bulk monoclonal products are stored in walk-in refrigerators for several months prior to vialing operations; data are not available to support the hold times for these bulk products.
 5. Failure to establish, maintain, and follow procedures for process validation in order to ensure that processes have been adequately validated and that the specified requirements continue to be met [21 CFR 820.75] in that;
 - a. the laminar air flow hoods in Vialing Rooms _____ and the biological safety cabinets in the Monoclonal Production Room have not been validated.

- b. cleaning validation has not been performed to demonstrate the effectiveness of cleaning of multi-use equipment or the removal of cleaning agent residue from equipment.
- 6. Failure to identify by suitable means the acceptance status of product [21 CFR 820.86] in that:
 - a. product was observed stored in walk-in refrigerators without designation as to the acceptance status of the product.
 - b. operators were observed tagging bulk red blood cells with a “released for vialing” sticker at the completion of the bulking process even though the bulk red blood cells had not yet been tested by Quality Control (QC).
- 7. Failure to establish and maintain acceptance procedures, where appropriate, to ensure that specified requirements for in-process product are met and to ensure that each production run, lot, or batch of finished product meets acceptance criteria [21 CFR 820.80(c) and (d)] in that:
 - a. there is no written procedure describing the method and documentation of visual appearance checks performed by operators on finished product following vialing. Furthermore, there is no documentation of the visual appearance check in the DHR.
 - b. sterility test samples that were not clearly labeled were observed being stored in the incubator; labeling on the individual test samples did not match labeling applied to the racks in which the samples were being stored
 - c. QC samples for testing of bulk reverse grouping cells were observed being stored in an unlabeled container in the QC refrigerator.
- 8. Failure to concurrently record the performance of each step in the manufacture and distribution of products [21 CFR 600.12(a)] in that operators in the Reagent Red Blood Cell Laboratory and the Monoclonal Production Room were observed recording monoclonal cell counts, used in determining cell viability, and critical calculations on scrap paper and later recording the final cell counts or final calculations in the device history record. The scrap paper on which the raw data and calculations were originally recorded were discarded.
- 9. Failure to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements, and to document the evaluation [21 CFR 820.50(a)]. The supplier of the media used for sterility testing of final product/environmental monitoring and the contract laboratory performing microbiological testing have not been evaluated.

10. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [21 CFR 820.70(g)] in that installation, operation, and performance qualification of the _____ Culture Systems and the _____ bioreactor, used in the production of monoclonal antibodies, have not been performed.
11. Failure to establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and the product or environment could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(d)] in that there is no written procedure describing proper attire to be worn by operators in the Monoclonal Production Room. Management stated that operators were required to wear hair covers, lab coats, and gloves; however, an operator was observed performing a manufacturing step without the required attire.

Neither the above violations nor the observations noted on the Form FDA 483 presented to your firm at the conclusion of the inspection are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations noted in this letter and the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing and quality systems. You are responsible for investigating and determining the causes of the violations identified by FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice. Such action includes license suspension and/or revocation; seizure; civil penalties and/or import alert, which would prevent your product from entering the U.S. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected.

We acknowledge receipt of your October 1, 1998, written response to the Form FDA 483. Our review finds your response adequate, but we have two comments. Relative to Form FDA 483 observation #51, we recommend that your revised SOP-I-007-0998-02, Calibration of Liquid Dispenser and Vial Fill Volumes, specify that sterilized graduated cylinders be used in the volume verification procedures. Transfer of non-sterile objects into the vialing rooms should be avoided whenever possible.

Additionally, relative to FDA 483 observation #63, it is unclear whether it is your intention to physically separate the Reagent Manufacturing Laboratory and Quality Control Laboratory from other areas of the facility. Please provide written clarification of your plans, including the basis for your decision to modify laboratories in a particular manner. You should respond to FDA in writing within 15 working days of receipt of this letter.

FDA will verify your implementation of promised corrective action during the next inspection of your facility. We do not expect a written response to this letter other than the information requested above. Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Anna Flynn at (301) 827-6213.

Sincerely,

A handwritten signature in black ink, appearing to read 'D. Michels', with a stylized flourish at the end.

Daniel L. Michels
Acting Director
Office of Regional Operations